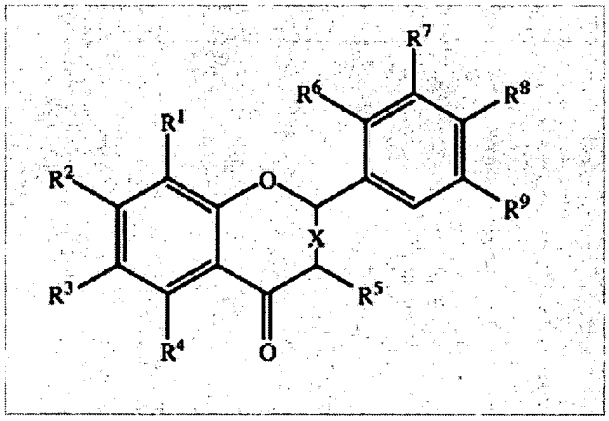
REMARKS

Applicant thanks the Examiner for a clarification of the generic claims and for a thorough examination. Claims 8-10 and 18-22 were pending following the last amendment. No claims are amended so Claims 8-10 and 18-22 remain pending.

The Examiner has rejected all of the pending claims as being unpatentable under 35 U.S.C. §103(a) as being unpatentable over **Bok et al.** (U.S. Patent No. 6,096,364). The Examiner concluded that this reference teaches that bioflavonoids of a particular structure (as follows):



are useful for lowering blood glucose levels. **Bok et al.** teaches that the most effective compounds are naringin, hesperidin and rutin; in fact, there is no demonstration that any other flavonoid is effective. Table II teaches that luteolin, quercetin, apigenin and kaemferol fall within the desired structural parameters. The Examiner concluded that dihydroxykaempferol would also fit into the listed structure.

The Examiner's obviousness case is predicated upon the idea that because **Bok et al.** demonstrated the effectiveness of certain bioflavonoids and

included a list of "preferred" flavonoids (without demonstration of effectiveness) one of skill in the art would be motivated to use any or all of the listed flavonoids with the reasonable expectation that blood glucose would be reduced thereby The Examiner further concluded that any mixture of the listed components that does not exhibit an unexpected result is obvious.

Applicant respectfully traverses this obviousness finding. The Examiner's obviousness case is based on the idea that one of ordinary skill in the art would be motivated to try the various flavonoids listed in Table II, and "[b]ecause all of the claimed flavonoids meet the criteria set out by Bok et al., the ordinary artisan would have a good expectation that each flavonoid would have individually performed successfully with regard to blood glucose lowering (treatment of diabetes)." Applicant respectfully contends that the art of biological effects of flavonoids is not sufficiently predictable that one of ordinary skill would reasonably have such expectations based on a mere unsubstantiated list that actually includes essentially all the most common flavonoids. Applicant will present data from the literature indicating a lack of predictability. Further, Applicant will point out that the instant application demonstrates that luteolin shows a level of effectiveness and activity not demonstrated by **Bok et al.** and not to be expected because of the teaching of that reference.

Structure I and Table II Include Essentially All Flavones and Flavonols

Applicant points out that the structure I taught by **Bok et al.** is far from a specific structure identifying a particular set of effective compounds. Rather this is the general three ringed backbone common to all flavones, flavanones and flavonols. Further, if a particularly effective subset of flavones, flavanones and flavonols were being taught, the description would not allow such a

breadth in terms of the R groups. A copy of the "USDA Database for the Flavonoid Content of Selected Foods" is presented for the Examiner's information. The Examiner will note that Table II of **Bok et al.** includes essentially all of the common dietary flavonoids. One of skill in the art of flavonoids would appreciate that far from teaching that structure I and Table II contains flavonoids especially suited to treatment of diabetes, structure I describes all flavanones, flavones and flavonols and Table II contains all of essentially all flavanoids common to the human diet. If this table teaches especially effective agents, such inclusiveness would not be expected. Applicant points out that **Bok et al.** specifically teaches the effectiveness of citrus peel and lists in Table I the bioflavonoids present in citrus peel. In the example portion of the patent **Bok et al.** shows experimental results only for citrus bioflavoids, namely naringin, hesperidin and rutin. Further, one sees from table II that the common thread between these demonstrated compounds is that they are all glycosylated. Rutin and hesperidin are rutinosyl glycosides while naringin is a rhamnosyl glycoside. Therefore, one of skill in the art would conclude that while **Bok et al.** provides a teaching regarding glycosides from citrus, it teaches nothing about the other flavonoids. A general list of common dietary flavonoids cannot teach anything specific.

The Biological Effects of Flavonoids are Highly Variable.

One of skill in the art would realize the incredible variability inherent in biological effects of flavonoids and lacking any experimental evidence would not expect any particular results from the compounds listed in Table II. Attached hereto is a selection of abstracts obtained by a quick search of Pub Med. One of ordinary skill would be familiar with all of these publications. In publication #1 twenty-one naturally occurring flavonoids were tested for

inhibition of alpha-glucosidase and alpha-amylase. Luteolin was the most effective—results varied widely from flavonoid to flavonoid. In publication #2 the free radical scavenging activity of four flavonoids (all coincidentally found in Table II) on preventing DNA damage was investigated. The protective activity of the flavonoids varied widely. At higher concentrations apigenein actually induced DNA breaks. In publication #3 the inhibitory effect of flavonoids on tyrosinase was investigated. The order of effectiveness was quercetin > galangin > morin > fisetin > 3,7,4-trihydroxyflavone > luteolin > apigenin > chrysin. In publication #4 the effects of flavonoids in inhibiting apoptosis resulting from peroxide was investigated. It was found that the flavanol (-)epigallocathechin gallate and the flavanol quercetin were effective in restoring cell viability (i.e., inhibiting apoptosis). However, the flavones luteolin, and apigenin increase apoptosis and the flavones hesperidin and narigin had no cytoprotective effects. In contrast publication #5 found that luteolin, quercetin and fisetin significantly decreased macrophage phagocytosis of myelin (an indication of inflammation). In publication #6 of the flavonoids investigated luteolin was the most effective in inhibiting nuclear factor-kappa B transcriptional activity. In publication #7 a clinical trail of a mixture of diosmin and hesperidin in Type 1 diabetics showed a reduction in glycation of hemoglobin but <u>was unrelated to glycaemic control</u>. These results are not exhaustive nor are they presented to demonstrate any particular effect of flavonoids. Rather, these publications show that biological effects of flavonoids are highly unpredictable. Depending on the system and the function being studied seemingly similar flavonoids may give very different results. Often the actual results are quite different from those initially expected by the scientists. Applicants respectfully contend that one of skill in the art would be well aware of the anomalous results obtained with flavonoids and without some demonstrated results (as in rutin, hesperidin and narigin) would

not expect the flavonoids of wide-ranging Table II to be effective in lowering blood glucose. In fact, it most likely that many of the compounds in Table II are ineffective in terms of lowering blood glucose.

Luteolin is effective on Diabetes.

Bok et al. present results only for hesperidin, narigin and rutin in lowering blood glucose levels. In example 2 a diet of 0.05% bioflavonoid is tested on streptozotocin-induced diabetes in rats. This treatment destroys the B cells and is essentially equivalent to Type 1 diabetes. Assuming that rats consume about 15g of chow a day this represents an intake of about 7.5 mg of bioflavonoid. According to **Bok et al.** this resulted in a 18-21% reduction in blood glucose after five weeks of treatment. The only results presented were for lowering blood glucose in chemically induced Type 1 diabetes.

In the application (page 18) genetically Type 1 rats were treated with 3 mg of luteolin and showed a 31% decrease in blood glucose within six hours. It would appear that the luteolin effect is more dramatic and much more rapid. In the application genetically Type 2 diabetic rats were treated with luteolin (page 18-19) and showed a decrease in blood glucose of between 10 and 28% in only 24 hours. When the treatments were extended to two weeks (Fig. 5) the rats showed decreases of 36-54% (average 41.1%). The luteolin gives greater effects, more rapidly and on both Type 1 and Type 2 diabetes animal models.

In **Bok et al.** male volunteers (apparently not diabetic) were treated for two months with 5-10 mg/kg of naringin, hesperidin or rutin and experience a 17-33% decrease in blood glucose.

In the application (pages 16-18), luteolin was administered to both Type 1 and Type 2 diabetics. The treatment resulted in a significant diminution in the amount of insulin needed and in drops of blood glucose level ranging from 57% to 155% Again, the luteolin effect is dramatic and is demonstrated with actual diabetics. In addition, the application describes amelioration of several other symptoms of diabetic disease—something not shown in **Bok et al.** The ability to ameliorate other symptoms of diabetes apart from blood glucose is the hallmark of a true method of treating diabetes.

Conclusion

Bok et al. showed that certain flavonoid glycosides reduce blood glucose in humans and in a Type 1 animal model. The unpredictable nature of biological results of flavonoids does not permit reasonable expectations of positive results from the unsubstantiated list of Table II. The instant application has show dramatic reduction of blood glucose in animal models of Type 1 and Type 2 diabetes. In addition, dramatic and rapid reduction of both blood glucose and other disease symptoms of diabetes has been demonstrated for both Type 1 and Type 2 human diabetics. **Bok et al.** fails to demonstrate any treatment of human diabetes.

In view of the foregoing, it is respectfully submitted that the application is in condition for allowance. Reexamination and reconsideration of the application, as amended, are requested.

If for any reason the Examiner still finds the application other than in condition for allowance, the Examiner is requested to call the undersigned attorney at the Los Angeles telephone number listed below to discuss the steps necessary for placing the application in condition for allowance.

You are hereby authorized to charge any fees due and refund any surplus fees to our Deposit Account No. 50-2567.

Respectfully submitted,

REED SMITH CROSBY HEAFEY

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Attachment:

Abstracts on flavonoid effects.
USDA Databse for The Flavonoid Content of Selected Foods.